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An analytical method for detecting toxic metal cations using cyclotrimeratrylene derivative capped gold nanoparticles

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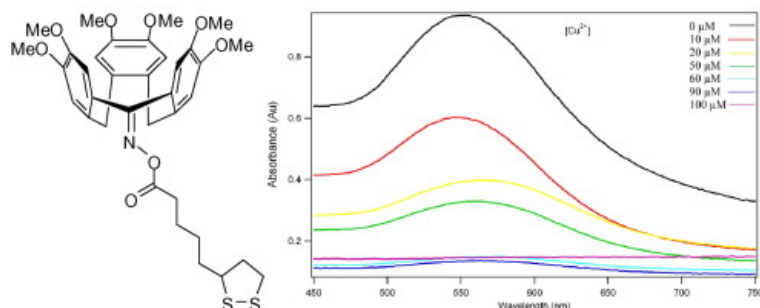
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Abstract

Cyclotrimeratrylene-oxime (CTV-oxime) derivatives that terminate with a dithiolate linker were synthesized enabling the supramolecular scaffold to adhere to gold nanoparticles (AuNPs) with the bowl-shaped cavity of the CTV scaffold exposed for utilization in host–guest chemistry. Exposure of these CTV functionalized AuNPs to varying concentrations of di- and trivalent metal cations resulted in the formation of large CTV-AuNP polymeric clusters and an accompanying a shift in the plasmon resonance. These interactions between the CTV-AuNPs and the metal cations in solution provides proof-of-concept that supramolecular functionalized AuNPs can be used as a simple and straightforward, on-site detection system for toxic metal cations in solution. The order of binding affinity of the metals studied based on observed K_d values is $\text{Cu}^{2+} > \text{Zn}^{2+} > \text{Pb}^{2+} > \text{Hg}^{2+} > \text{Eu}^{3+} > \text{Cd}^{2+}$.

Graphical abstract



Keywords

Gold nanoparticles, Supramolecular chemistry, Heavy metal detection, Lanthanides, Cyclotrimeratrylene

Introduction

Due to the environmental and biological impact of metal ion contamination, the development of sensitive and selective detection systems for colorless metal ions is of great importance. The toxicity of heavy metals is well known, yet even essential metals are toxic at higher concentrations including zinc¹ and also copper, which is implicated in neurodegenerative diseases.² A variety of analytical devices have been developed for the detection of metal ions, including systems based on direct chemosensors,³ atomic fluorescence spectrometry (AFS),⁴ inductively coupled plasma mass spectrometry (ICP-MS),⁵ and atomic absorption spectroscopy (AAS).⁶ Although these techniques offer sensitive and selective analytical approaches, they are expensive, require sophisticated equipment, and lack the portability for on-site detection.

Unlike traditional organic fluorescent dyes, gold nanoparticles (AuNPs) have much stronger molar absorptivities that are 3–5 orders of magnitude higher than organic fluorescent dyes^{7, 8} and are of great interest in chemical and biological sensing⁹ as well as for in vitro diagnostics.¹⁰ The optical properties of AuNPs are due to their unique surface plasmon resonance (SPR) where electrons on the surface of a AuNP are in collective oscillation and become in resonance with incident electro-magnetic radiation.^{11, 12} Modified AuNPs make excellent colorimetric analytical platforms because AuNP aggregation due to analyte detection results in a distinct color change from red to blue.^{13, 14, 15, 16} AuNPs with various surface-bound ligands have been previously employed to detect K^+ ,¹⁷ and Ca^{2+} ,¹⁸ divalent heavy metals (Hg^{2+} , Pb^{2+} , Cd^{2+}),^{19, 14} Cr^{3+} ,²⁰ and trivalent lanthanide ions.²¹ Herein we describe cyclotrimeratrylene (CTV)-functionalized AuNPs that provide the basis for the design of an analytical tool that can be used for the detection of di- and trivalent metal ions in solution for the detection of metal ions of environmental concern.

Cyclotrimeratrylene (CTV, Fig. 1) is a bowl-shaped supramolecular scaffold^{22, 23} that we have previously employed through apex derivatization to provide a supramolecular scaffold with the concave bowl receptor pointed *away* from the surface, enabling CTV to function as a gold surface-bound host molecule.²⁴ The crown and saddle conformers are comparable in energy and interconvert in solution.²⁵

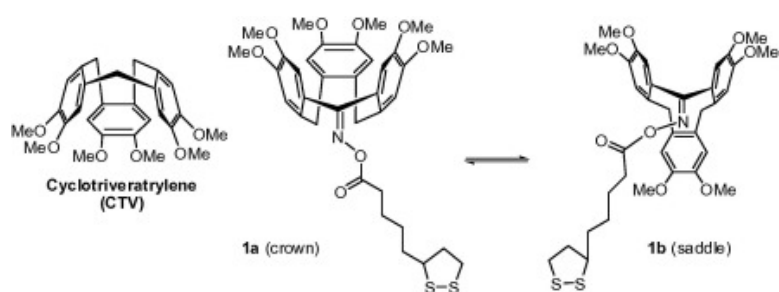
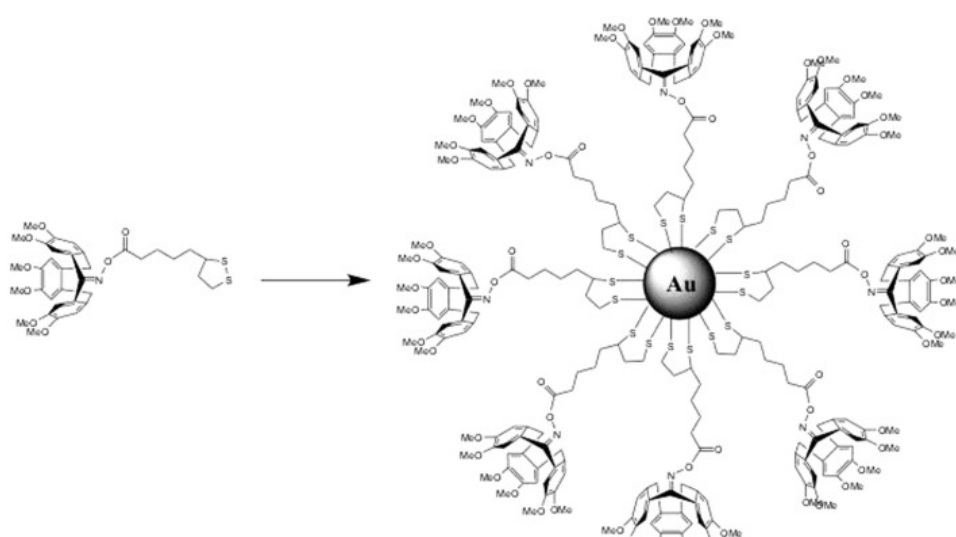


Figure 1. CTV, and apex-modified CTV-oxime lipoate ester.

CTV derivatives have been shown to bind both divalent and trivalent metal ions with their peripheral ortho dimethoxy ether groups creating coordination polymers as well as clathrate crystalline materials.^{26, 27} Hardie and co-workers obtained crystal structures of CTV bound to alkali-earth metal cations (Na^+ , K^+ , Rb^+ , and Cs^+)²⁸ forming large crystalline coordinate polymers through binding the methoxy group of CTV, and revealed that lanthanide metal ions can also bind to CTV-methoxy groups.²⁹ X-ray crystallographic data on CTV-lanthanide complexes indicated that the water molecules of the capped triangular dodecahedral $[\text{Eu}(\text{H}_2\text{O})_9]^{3+}$ cations are at distances favorable for hydrogen bond formation with the CTV perimeter methoxy lone-pairs. Combining these technologies, we designed a colorimetric analytical device for the detection of di- and trivalent metal ions employing CTV bound to gold nanoparticles (AuNP). An apex-modified CTV supramolecular scaffold head group with a dithiolane tail installed as the lipoic acid ester of CTV oxime for binding to a gold surface with the CTV bowl shaped cavity directed *away* from the surface was synthesized and bound to AuNPs.

Results and discussion

With the successful design and synthesis of an apex modified CTV supramolecular scaffold head group with a dithiolane tail, 15 nm AuNPs were functionalized by the addition of a 2.7 mM solution of CTV-dithiolane ligand **1a/b** in a 1% polysorbate 20 acetonitrile (ACN) solution (Scheme 1).¹³ These samples were then vortexed for 20 s to ensure homogeneity throughout the solution. The AuNP/CTV-dithiolane solution was allowed to sit at room temperature for ~24 h to allow full functionalization of the AuNPs. In order to remove the excess CTV-dithiolane, the AuNPs were centrifuged at 14,000 rpm for ~30 min. The dense CTV-dithiolane functionalized AuNPs precipitated and the excess CTV-dithiolane remained in solution. The supernatant was carefully removed and the functionalized AuNPs were resuspended in a 1% polysorbate 20/ACN solution. This process was repeated three times to ensure complete removal of any excess CTV-dithiolane from the AuNP solution. Transmission electron microscopy (TEM) was used to confirm that the AuNPs were intact after functionalization with the CTV-dithiolate ligand (Fig. 2). TEM images reveal that the CTV-functionalized AuNPs retain their roughly spherical shape. Due to the differences in the refractive indices between the water and acetonitrile solvents, the UV-Vis spectra were red shifted upon modification of AuNPs with CTV in ACN. The SPR maximum absorbance of the AuNP solution had shifted from 522 nm in water to the expected 550 nm in ACN solution (Fig. 3).³⁰ The decrease in absorbance is due to the loss of nanoparticles from the washing and extracting of solvent to remove excess CTV after modification.



Scheme 1. Route to functionalizing the AuNPs with the CTV-dithiolane ligand.

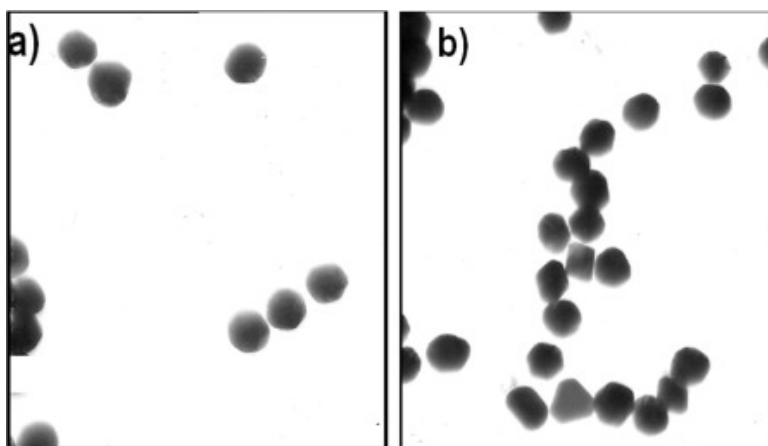


Figure 2. TEM images (a) unfunctionalized and (b) of the CTV-dithiolate functionalized AuNPs show that after modification, the AuNPs retain their spherical shape and show that the CTV-lipoate AuNPs do not polymerize without the addition of metal cations.

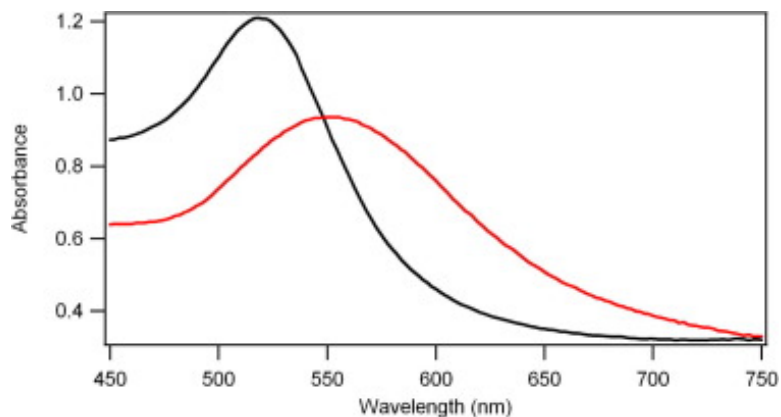


Figure 3. UV-Vis spectra of the unmodified nanoparticles purchased from Ted Pella (black) versus the CTV-lipoate modified AuNPs in 1% polysorbate 20/ACN (red) showing that modification of the AuNPs with the CTV-lipoate moiety and the subsequent solvent change results in a decrease and shift in absorbance from 522 nm to 550 nm.

With the successful functionalization of stable CTV-dithiolane 15 nm AuNPs, a series of colorless di- and trivalent metal ions (Cu^{2+} , Pb^{2+} , Hg^{2+} , Zn^{2+} , Cd^{2+} , and Eu^{3+}) were titrated into a solution of CTV-dithiolane modified AuNPs in polysorbate 20/ACN. Various concentrations of each metal ion (0 μM , 10 μM , 20 μM , 50 μM , 60 μM , 90 μM , and 100 μM) in nanopure water were pipetted into the CTV-dithiolane AuNP solution. The solution was incubated at room temperature ($\sim 21^\circ\text{C}$) in order to allow for complexation between CTV-methoxy moieties and the divalent and trivalent metal cations, which resulted in the formation of a purple precipitate. The system was responsive to varying metal ion concentrations as evidenced by recording the UV–Vis spectrum of the supernatant between 450 and 750 nm. Typical UV–Vis spectra are shown in Fig. 4a–c. The initial absorbance of the CTV-dithiolane functionalized 15 nm AuNPs which was monitored at 550 nm decreases accompanied by broadening as the metal ion concentration is increased from 10 to 100 μM . A decrease in absorbance at 550 nm and the observed precipitate are consistent with metal cation binding to CTV methoxy groups in an intra-NP fashion resulting in the formation of a metal ion assisted polymerization of the CTV-dithiolane modified AuNPs. Evidence of the formation of a metal ion-CTV-AuNP polymerization was obtained from TEM images (Fig. 5).

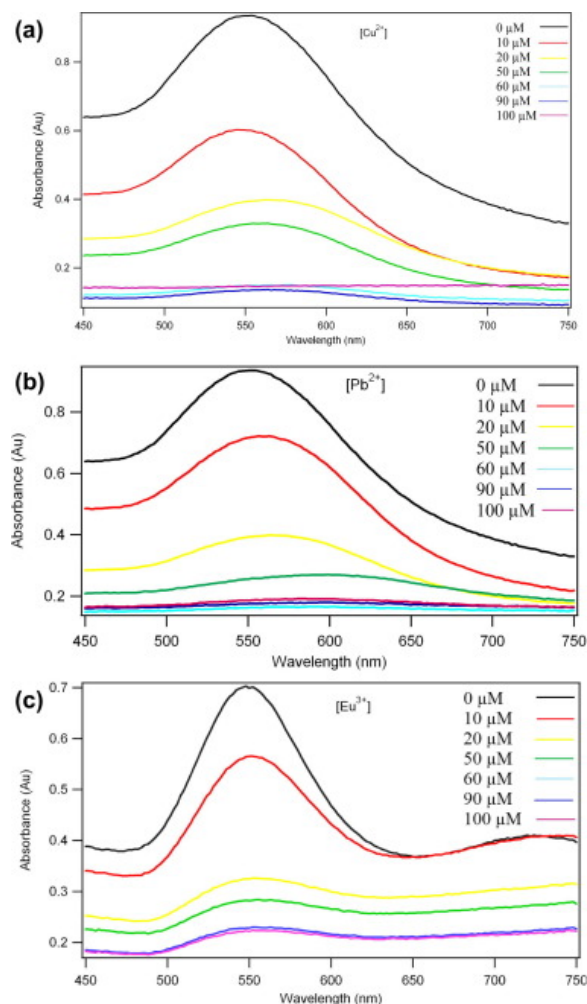


Figure 4. Typical spectroscopic metal binding titrations of increasing (a) $[\text{Cu}^{2+}]$, (b) $[\text{Pb}^{2+}]$, and (c) $[\text{Eu}^{3+}]$ binding to 15 nm CTV-dithiolane functionalized AuNPs resulting in a decrease in absorbance after 24 h.

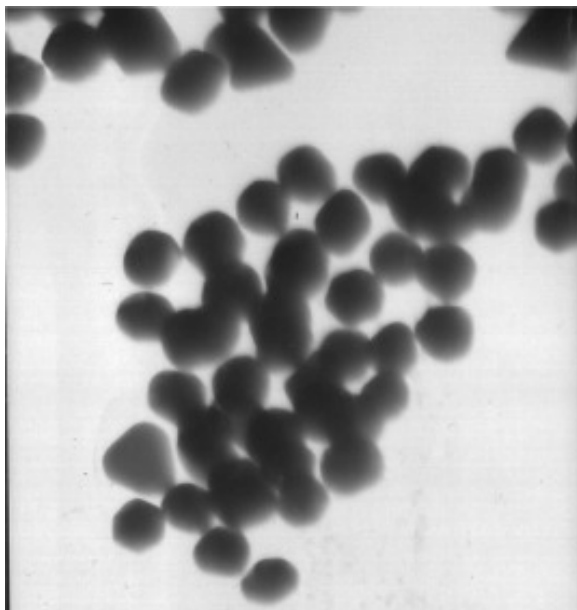


Figure 5. TEM image of the observed CTV-dithiolane AuNP precipitate upon exposure to metal analytes.

Metal cation affinities to the methoxy moieties of the CTV-dithiolate functionalized AuNPs were determined by titrating metal ions into a CTV-dithiolane functionalized AuNP solution and monitoring the decrease in absorbance at 550 nm (Fig. 4a–c). Dissociation constants (K_d) for a single metal binding event were determined by fitting plots of absorbance versus. metal ion concentration to Eq. 1,³¹ where p is the number of sites

$$r = pC_m/(K_d + C_m) \quad (1)$$

for which the interaction with the metal cation is governed by the intrinsic dissociation constant, K_d , and r is the binding function calculated by subtracting the metal titration absorbance, Ab_m , at 550 nm from the initial absorbance, Ab_i using Eq. 2. C_m is the

$$r = Ab_i - Ab_M \quad (2)$$

concentration of the metal ion that was titrated into the AuNP solution. A value for K_d was obtained by fitting the data via an iterative process that allowed both K_d and p values to vary (Fig. 6a–c). The best fits obtained provided p values that ranged from 0.3 to 1.4 and K_d values that ranged from $13 \mu\text{M} \pm 1$ for Cd^{2+} to $60 \mu\text{M} \pm 1$ for Cu^{2+} (Table 1). Based on these K_d values, a binding affinity series was created represented by the following order: $\text{Cu}^{2+} > \text{Zn}^{2+} > \text{Pb}^{2+} > \text{Hg}^{2+} > \text{Eu}^{3+} > \text{Cd}^{2+}$.

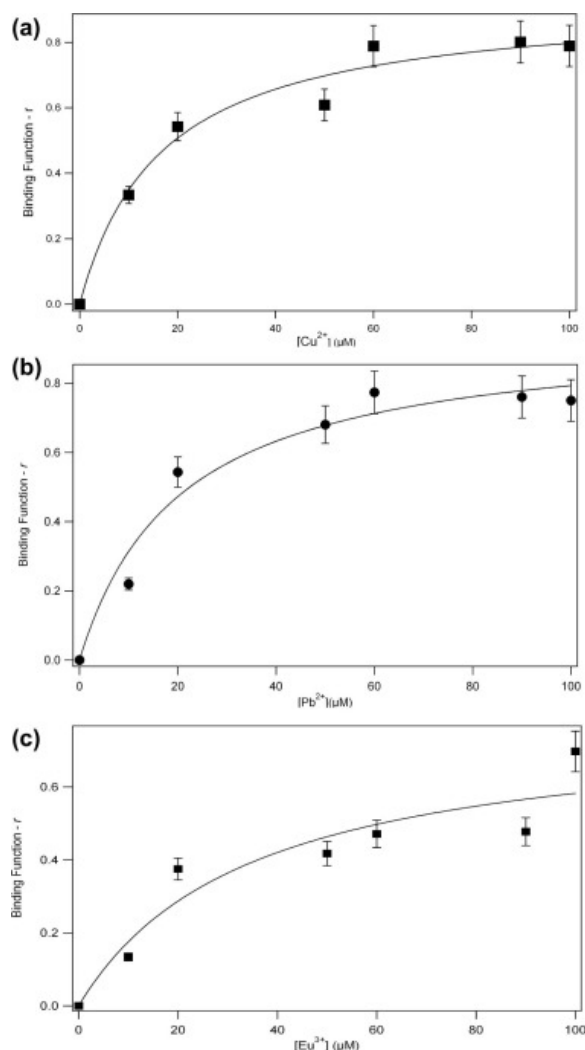


Figure 6. Plot of binding function r versus C_m (the concentration of the metal ions in the solution) for (a) Cu^{2+} , (b) Pb^{2+} , and (c) Eu^{3+} titrated with CTV-dithiolate AuNPs.

Table 1. Metal binding affinity data for varying metals titrated with CTV-lipoate AuNPs

Metal	p	K_d (μM)	σ (\pm)	χ^2
Pb^{2+}	1.0	49 ± 1	2	0.020
Cd^{2+}	1.4	13 ± 1	1	0.069
Zn^{2+}	0.5	51 ± 3	3	0.014
Cu^{2+}	0.9	60 ± 1	1	0.013
Hg^{2+}	0.3	34 ± 1	1	0.011
Eu^{3+}	0.8	29 ± 2	2	0.033

Since the divalent metal ions used can adopt four, five, or six coordinate geometries in solution whereas Eu^{3+} can exhibit coordination geometries of 8 or higher, we hypothesized that the metal ions coordination sphere is made up of CTV-methoxy oxygens and water molecules.³² Evidence for the possibility of such a structure in the aggregation of CTV-decorated AuNPs is suggested by X-ray crystallographic data of a Na^+ bound CTV complex.³³ In this structure, each Na^+ ion coordinates to symmetry-equivalent CTV molecules resulting in the Na^+ cation residing in a highly distorted octahedral geometry where each CTV molecule chelates edge-bound to Na^+ through one dimethoxy moiety and *cis* water/hydroxy ligands. An even better precedent than the harder alkali metal binding is the softer Ag^+ binding to the methoxy ether oxygens of CTV.^{34, 35} Likewise, the X-ray crystal

structures of the Cs^+ and Rb^+ CTV complexes revealed that both of the larger monovalent cations may bind to the dimethoxy moieties of CTV and two *cis* water/hydroxyl ligands forming a highly distorted six-coordinate complex in a similar fashion to Na^+ .²⁸ Interestingly, the X-ray structure of the Eu^{3+} CTV complex indicates that the methoxy moieties act as hydrogen bond acceptors with the aquo ligands of the $[\text{Eu}(\text{H}_2\text{O})_9]^{3+}$ cations forming hydrogen-bonded superstructures.²⁹ The $[\text{Eu}(\text{H}_2\text{O})_9]^{3+}$ cations reside in two distinct environments but both retain their water ligands and do not form direct bonding interactions with the methoxy moieties of CTV. We hypothesize that the CTV-dithiolane functionalized AuNPs may form similar clusters that link the AuNPs.

The binding mode observed for Eu^{3+} , while different from that observed for the alkali metal ions, is likely the result of the more Lewis acidic Eu^{3+} ion versus the M^{2+} cations examined. Since methoxy moieties are not as strong a Lewis base as water molecules, the highly Lewis acidic Eu^{3+} cation would likely preferentially bind to water over CTV methoxy groups.³⁶ Therefore, one would expect that the observed K_d value of $29 \pm 2 \mu\text{M}$ for Eu^{3+} results from the $[\text{Eu}(\text{H}_2\text{O})_9]^{3+}$ cation hydrogen-bonding with the methoxy moieties of CTV, similar to the reported CTV- Eu^{3+} X-ray crystal structure. For the remaining divalent transition metal complexes capable of forming octahedral complexes in solution (Cd^{2+} , Pb^{2+} , Cu^{2+}), all three are intermediate to soft metal acids and exhibit p values of ~ 1 . The K_d values for these three complexes increase with increasing hardness of these soft metal acids, suggesting that the softer the metal ion the better affinity for a methoxy ligand. Therefore, it was hypothesized that these three metal ions will be chelated by some combination of CTV-methoxy groups and water molecules (Fig. 7), similar to the alkali metal cations. Likewise, the soft metal acids Hg^{2+} and Zn^{2+} likely bind to the CTV-methoxy groups and water molecules in some combination, similar to the alkali metal cations, since the softer Hg^{2+} ion binds more tightly ($34 \pm 1 \text{ nM}$) than Zn^{2+} ($51 \pm 3 \mu\text{M}$). However, the observed p values for these two divalent metal ions are 0.3 and 0.5, respectively, indicating a difference in the type of polymeric structure formed upon binding. The Hg^{2+} and Zn^{2+} ions may prefer tetrahedral geometries, although other geometries are possible, so an altered superstructure is not unexpected.

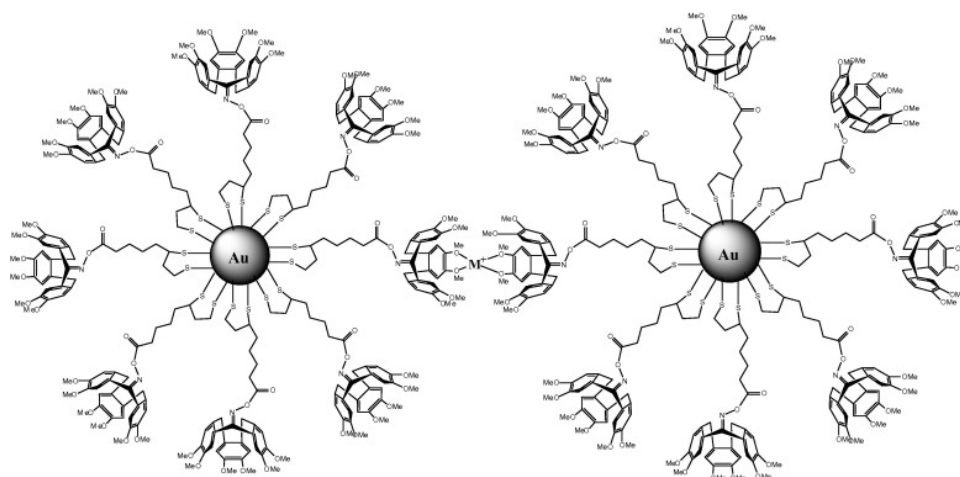


Figure 7. Proposed binding interaction between a metal cation and the CTV-methoxy ligand in solution, forming insoluble AuNP based polymer aggregates.

In summary, an apex-modified CTV derivative containing a dithiolane tail was used to functionalize 15 nm AuNPs to afford a colorimetric analytical method to determine the metal binding properties of a series of di- and trivalent metal ions in solution. While previously-reported devices allow for the detection of metal ions in solution, no determination of metal ion binding constants was reported. The CTV-AuNP method that we report herein offers an advantage as being able to both detect and analytically quantify metal ion concentrations in the solution. This spectroscopic method provides a prototype for a new method to analyze metal cations in solution.

Acknowledgments

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